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Position Document 1

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ETHYLENE DIBROMIDE

POSITION DOCUMENT I

Ethylene Dibromide (EDB) Working Group

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U.S. Environmental Protection Agency

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Preliminary Risk Assessment: Examination of possible unreasonable risks associated with uses of pesticide and a gathering of all available information to determine whether or not this or any other risk does exist. Initiates literature search and evaluates risk data. Limited information on exposure to forecast extent of risk.

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I. BACKGROUND

A. Characteristics

1. Nomenclature:

Ethylene dibromide (EDB) is the common or trivial name for 1,2-dibromoethane. It is a soil and commodity fumigant having both nematocidal and insecticidal uses. Its EPA pesticide number is 042002; NIOSH number is KH92750; and Chemical Abstract System (CAS) number, listed under Ethane, 1,2,-dibromo, is 0001060934.

In this document the term EDB refers specifically to the organic molecule ethylene dibromide and does not include inorganic bromide(s) or total bromide(s). These latter two terms are used in the food additive tolerances (21 CFR 123) and raw agricultural commodities tolerances (40 CFR 180). Furthermore there are uncertainties in portions of the scientific literature on ethylene dibromide as to which entity is measured analytically and reported as residues. The language of the food tolerances was originally based on the rationale that the parent compound, EDB, was converted to inorganic bromide ions following soil or commodity fumigation. Also the analytical methods generally employed up to 1969 had sensitivities of 0.2 to 1.0 ppm (parts per million) and frequently did not identify or differentiate between the organic or inorganic bromides in the sample.

2. Chemistry:

EDB, a colorless, heavy non-flammable liquid at room temperature, is prepared commercially by reacting bromine with ethylene gas. It has a characteristic mildly sweet odor detectable in air at levels ranging from 10 to 25 ppm (77 mg/M^3 to 192.5 mg/M^3). Its chemical formula is CH_2BrCH_2Br and its molecular weight is 187.88.

EDB melts at 9.6°C and boils at 131.4°C; its heat of vaporization is +53 cal./gm at 25°C, but it has no flash point. Its vapor pressure

is 11.0 mm Hg at 25°C and its vapor density is 6.5 (air=1). The density of EDB saturated air is 1.08 (air=1) and, at saturation, the concentration of EDB is 1.3% by volume at 25°C. The viscosity of EDB is 1.65 centipoise at 20°C and its density is 2.18 g/ml at 20°C. EDB is soluble in ethanol and ethyl ether and its solubility in water is 0.43 g/100g at 30°C. One part per million (ppm) of EDB is equivalent to 7.68 mg per cubic meter in air and one mg EDB per cubic meter is equivalent to 0.13 ppm.

B. Registered Products and Uses

1. Number of Products and Production

There are 122 Federal pesticide registrations, held by 53 registrants, of products containing EDB as an active ingredient. In addition, there are 24 State registrations, held by 12 registrants, of products containing EDB as an active ingredient. There are no Federally registered products containing EDB as an inert ingredient. Most of the Federal-and State-registered products are mixtures of EDB and other active ingredients such as carbon tetrachloride, ethylene dichloride, methyl bromide, chloroform, carbon disulfide, sulfur dioxide, chloropicrin, and benzene. EDB is usually formulated as a liquid concentrate or as a gel.

The U. S. production of EDB, as shown by the Stanford Research Institute (SRI) for 1973, 1974, 1975, was 331.1, 332.1, 275.2 million pounds, respectively, with an estimated one third of the 1973 production (approximately 100 million lbs) being shipped overseas (SRI, 1975).

2. Use Patterns

The primary pesticidal uses of EDB are:

- Pre-plant soil fumigation by injection for a wide variety of food and non-food crops including vegetables, fruits, grains peanuts, cotton, and tobacco;
- Post-harvest commodity fumigation for grains, fruits and vegetables (an important current use as a commodity fumigant appears

to be in connection with various State, Federal or international quarantine programs on citrus, stone -, and other fruits, nuts, and vegetables);

- o Fumigation of grain milling machinery and flour mills to control insect infestations in milling residues and unprocessed milled products.

There are several minor uses including:

- o Control of mountain pine bark beetles in the Western States by Federal and State forestry agencies;
- o Control of dry-wood and subterranean termites in structural pest control operations;
- o Control of wax moth in honey combs;

An internal preliminary economic review of EDB, prepared from very limited data, estimated that 7,306,000 lbs. of EDB pesticides (3-4% of 1975 domestic production) are used annually. The breakdown of this use by use-pattern is presented in Table 1.

Table 1 - Estimated current pesticidal use of EDB.

Use	Thousand pounds/Yr
Tobacco*	4,059
Vegetable*[1/]	1,000[2/]
Peanuts*	384
Cotton	700
Grain storage**	666
Flour milling**	385
Quarantine**	78[3/]
Wax moth/honeycombs	17.6
Mountain pine bark beetle	17.5
Subterranean termite control	5

*Soil fumigation - nematode control
**Commodity fumigation - insect control
1/ includes fruits (orchard) and nuts
2/ California uses estimated to total 400,000 lbs./yrs
3/ Estimate from APHIS, USDA, Sept., 1977

The major domestic producers of EDB, as a pesticide, are Great Lakes Chemical Corp.; Velsicol Chemical Corp. (formerly Michigan Chemical Corp.); and, up to August 1977, Dow Chemical.* The bulk of EDB domestic production is used as a gasoline additive and a minor amount is used in industrial and pharmaceutical processes.

3. Tolerances

There are no tolerances for EDB per se in or on raw agricultural commodities because it was concluded on the basis of data originally submitted by petitioners, that no EDB residues would result. This was based on the rationale that the parent EDB compound released bromide ions which were fixed in soils and subsequently taken up by plants as inorganic bromide, and also that residue analyses, then available for organic bromides in crops grown in treated soil, were negative. The analytical method employed at that time for organic bromide had a sensitivity of 0.2 to 1.0 ppm (parts per million) and was based on potentiometric titration which was not specific for EDB per se, but rather measured any organic bromide which was extracted by the procedure and not lost in cleanup steps. Consequently, tolerances or exemption from tolerance for use of EDB in or on raw agricultural commodities resulting from its use either as a pre-harvest soil fumigant or as a post-harvest commodity fumigant were established in 40 CFR 180. Food additive tolerances for inorganic bromides resulting from use of EDB are listed in 21 CFR 123 and 561. The Food and Drug Administration (FDA) and EPA are currently reviewing standards for tolerance setting for organic bromide compounds and inorganic bromide residues.

Tolerances for residues of inorganic bromides [calculated as Br] in or on raw agricultural commodities grown in soil treated with the nematocide EDB were established in 40 CFR 180.126 as:

- 75 ppm in or on broccoli, carrots, melons, parsnips, potatoes;

* On Aug. 5, 1977, Dow announced by letter that they were withdrawing from the EDB pesticide market (Dow, 1977).

- 50 ppm in or on eggplant, okra, summer squash, sweet corn, sweet corn forage, sweetpotatoes, tomatoes;

- 40 ppm in or on pineapple;

- 30 ppm in or on cucumbers, lettuce, peppers;

- 25 ppm in or on cottonseed, peanuts (180.126a restricts use of treated peanut hay and hulls as feed for meat and dairy animals);

- 10 ppm in or on asparagus, cauliflower;

- 5 ppm in or on lima beans, strawberries.

Tolerances for residues of inorganic bromides in or on raw agricultural commodities resulting from post-harvest fumigation with EDB were established in 40 CFR 180.146 as:

- 50 ppm [calculated as Br] in or on barley, corn, oats, popcorn, rice, rye, sorghum (milo), wheat;

- 25 ppm [calculated as total combined bromine from both inorganic and organic compounds] in or on cherries and plums (fresh prunes) in accordance with specified quarantine programs;

- 10 ppm [calculated as Br] in or on string beans, bitter melons (Mormodica charantia), cantaloupes, Cavendish bananas, citrus fruits, cucumbers, guavas, litchi fruit, litchi nuts, longan fruit, mangoes, papayas, bell peppers, pineapples, and zucchini squash in accordance with specified quarantine programs.

An exemption from tolerance for residues of organic bromide from post-harvest fumigation with EDB is established in 40 CFR 180.1006 for barley, corn, oats, popcorn, rice, rye, sorghum (milo), wheat.

A food additive tolerance for inorganic bromide residues from the use of EDB in or on grain-mill machinery, is established in milled fractions, derived from all sources, at 125 ppm by 21 CFR 123.225 [calculated as Br].

A food additive tolerance for inorganic bromide residues from the use of a mixture of EDB and methyl bromide in the production of fermented malt beverages is established in 21 CFR 123.230 as 125 ppm [calculated as Br]. An additional 25 ppm of inorganic bromides from other sources is established in 21 CFR 123.230d.

Food additive tolerances for inorganic bromides resulting from all organic bromides used as a soil fumigant (nematocide), raw agricultural commodity fumigant or processed food fumigant are established in 21 CFR 123.250 as:

- 400 ppm in or on dried eggs and processed herbs and spices;
- 325 ppm in or on parmesan cheese and roquefort cheese;
- 250 ppm in or on concentrated tomato products and dried figs;
- 125 ppm in or on processed foods;
- 125 ppm in or on bread, biscuit, cake, cookie, and pie mixes; breading; cereal flours and related products; cracked rice; dried vegetables; flours of barley, milo (sorghum), oats, rice, and rye; macaroni and noodle products; and soy flour.

Food additive tolerances for residues of inorganic bromides from fumigation with EDB are established in 21 CFR 561.260 as:

- 125 ppm for residues in or on milled fractions for animal feed from barley, corn, grain sorghum (milo), oats, rice, rye, and wheat, resulting directly from fumigation with methyl bromide or from carryover and concentration of residues of inorganic bromides from fumigation of the grains with methyl bromide or EDB.

4. Regulatory History as a Pesticide

Date:	Action or Recommendation
7/29/55	Pesticide Petition submitted by Dow Chemical Co. to FDA requesting establishment of tolerances for inorganic bromide residues resulting from soil application of EDB found in or on the following commodities: milk (30 ppm), peanuts (30 ppm), peanut hay (30 ppm), asparagus (10 ppm), carrots (100 ppm), cauliflower (10 ppm), celery (100 ppm), corn (50 ppm), cottonseed (200 ppm), lettuce (20 ppm), lima beans (5 ppm), parsnips (25 ppm), white potatoes (75 ppm), strawberries (5 ppm), sugar beets (5 ppm), sugar beet tops (100 ppm), sweet potatoes (50 ppm), and turnips (75 ppm).
8/30/55	Dow Chemical Co. amended petition by dropping tolerance requests for milk, peanuts and peanut hay due to inadequate data on animals fed peanuts and peanut hay grown on soil treated with EDB and because bromine residues in peanut hay fed to dairy cattle might contaminate milk.
9/29/55	Federal Register notice published proposing establishment of tolerances for inorganic bromide residues resulting from soil application of EDB found in or on the following commodities: asparagus (10 ppm), carrots (100 ppm), cauliflower (10 ppm), celery (100 ppm), corn (50 ppm), cottonseed (200 ppm), lettuce (20 ppm), lima beans (5 ppm), parsnips (25 ppm), white potatoes (75 ppm), strawberries (5 ppm), sugar beets (5 ppm), sugar beet tops (100 ppm), sweet potatoes (50 ppm), and turnips (75 ppm).
1/26/56	Dow Chemical Co. amended petition[1/] to exclude tolerance requests for lettuce, potatoes, turnips, celery, corn and sugar beets due to lack of adequate residue data.

[1/] Tolerances from this petition (7/29/55) never officially established.

6/8/56 Pesticide Petition submitted by Dow Chemical Co. requesting that EDB be exempted from the requirements of a tolerance when used as a post harvest fumigant for the following raw agricultural commodities: wheat, barley, oats, rye, corn (including popcorn and sweet corn) and grain sorghum (milo).

7/26/56 Federal Register notice published establishing an exemption from tolerance requirements for EDB when used as a post-harvest fumigant on the following grains: wheat, barley, oats, rye, corn (including popcorn and sweet corn) and grain sorghum (milo).

7/26/56 Federal Register notice published establishing a tolerance of 50 ppm for inorganic bromide residue, resulting from post-harvest fumigation with EDB, in or on the following grains: wheat, barley, oats, rye, corn (including popcorn and sweet corn) and grain sorghum (milo).

8/1/56 USDA petitioned FDA for the continued use of EDB as a fumigant in two emergency programs designed to control the widespread introduction of the fruit fly into large agricultural regions of the U.S. and for the establishment of a tolerance of 10 ppm inorganic bromide residue, resulting from fumigation with EDB by the USDA-sponsored program, found in or on beans (string), bitter melon, Cavendish bananas, citrus fruits, cucumbers, guavas, mangoes, papayas, peppers (bell), pineapples and zucchini squash.

9/22/56 Federal Register notice published establishing tolerance of 10 ppm for inorganic bromide residue, resulting from fumigation with EDB, found in or on beans (string), bitter melon, Cavendish bananas, citrus fruits, cucumbers, guavas, mangoes, papayas, peppers (bell), pineapples and zucchini squash.

10/14/56 Pesticide Petition submitted by Dow Chemical Co. to FDA requesting tolerances for inorganic bromide residues resulting from soil application of EDB on the following raw agricultural commodities: cucumber (30 ppm), lettuce (30 ppm), peppers (30 ppm), eggplant (50 ppm), summer squash (50 ppm), tomatoes (50 ppm), broccoli (75 ppm), melons (75 ppm), Irish potatoes (75 ppm), cabbage (100 ppm), green beans (100 ppm), and celery (200 ppm).

1/3/57 Federal Register notice published proposing establishment of tolerance of 10 ppm for inorganic bromide residue, resulting from fumigation with EDB, found in or on cantaloupes and litchi nuts.

1/17/57 USDA petitioned FDA to establish a tolerance of 20 ppm for total bromide residues resulting from fumigation with EDB in or on plums treated as part of a quarantine program for fruit fly-infested fruit imported from Mexico.

3/7/57 Federal Register notice published proposing establishment of tolerances for inorganic bromide residues resulting from soil application of EDB on the following raw agricultural commodities: cucumber (30 ppm), lettuce (30 ppm), peppers (30 ppm), eggplant (50 ppm), summer squash (50 ppm), tomatoes (50 ppm), broccoli (75 ppm), melons (75 ppm), Irish potatoes (75 ppm), cabbage (100 ppm), green beans (100 ppm), and celery (200 ppm).

4/5/57 Federal Register notice published proposing establishment of a tolerance of 20 ppm for inorganic bromide residues, resulting from fumigation with residues with EDB, found in or on plums treated with EDB, as part of a quarantine program.

5/14/57 Dow Chemical Co. amended petition to exclude tolerance requests for inorganic bromide residues on the following commodities: Irish potatoes, cabbage, green beans and celery.

5/28/57 Federal Register notice published establishing the following tolerances for inorganic bromide residues resulting from post-harvest application of EDB: 10 ppm found in or on cantaloupes and litchi nuts and 20 ppm found in or on plums.

6/18/57 Federal Register notice published establishing tolerance for inorganic bromide residues resulting from soil application of EDB in or on the following commodities: cucumbers (30 ppm), lettuce (30 ppm), peppers (30 ppm), eggplant (50 ppm), summer squash (50 ppm), tomatoes (50 ppm), broccoli (75 ppm), and melons (75 ppm).

1/21/58 Pesticide Petition submitted by Dow Chemical Co. to FDA requesting establishment of tolerances for inorganic bromide residues resulting from soil application of EDB found in or on the following raw agricultural commodities: okra (50 ppm) and pineapples (40 ppm).

2/15/58 Federal Register notice published proposing establishment of tolerances for inorganic bromide residues for the following commodities: okra (50 ppm) and pineapples (40 ppm).

3/13/58 Federal Register notice published proposing establishment of a tolerance of 10 ppm for inorganic bromide residues, resulting from fumigation with EDB, found in or on litchi fruits.

5/2/58 Federal Register notice published establishing tolerance of 10 ppm for inorganic bromide residues, resulting from fumigation with EDB, found in or on litchi fruits.

6/7/58 Federal Register notice published establishing tolerances for inorganic bromide residues for the following commodities: okra (50 ppm) and pineapples (40 ppm).

5/10/58 Pesticide Petition submitted by Dow Chemical Co. to FDA requesting establishment of tolerance for inorganic bromide residues, resulting from soil application of EDB, found in or on the following commodity: potatoes (75 ppm).

7/4/58 Federal Register notice published proposing establishment of a tolerance for inorganic bromide residues of 75 ppm found in or on potatoes.

10/4/58 Federal Register notice published establishing tolerance for inorganic bromide residues, resulting from soil application of EDB, found in or on the following commodity: potatoes (75 ppm).

10/26/64 Pesticide Petition submitted by Dow Chemical Co. to FDA requesting establishment of tolerances for inorganic bromide residues, resulting from soil application of EDB, found in or on the following raw agricultural commodities: peanuts (25 ppm).

4/1/65 Dow Chemical Co., amended use directions found on the labels of EDB products used to treat soil for cultivation of peanut crops to include the following: "Any forage crop grown on soil treated with a bromide containing fumigant should not be used as a feed for dairy animals, or for animals being finished for slaughter until 2 years after row treatments are made and 3 years following overall treatments."

5/28/65 Pesticide Petition submitted by USDA to FDA requesting establishment of a tolerance increase from 10 ppm to 50 ppm for inorganic bromide residues in or on Mexican oranges treated with EDB.

6/65 National Academy of Sciences/ National Research Council (NAS/NRC) issued a report recommending that "no residue" and "zero tolerance" concepts be abandoned. Report stated that zero tolerances were not desirable, since, as experience bore out, residues might be present at levels below the current sensitivity of detection methods.

11/9/65 Federal Register notice published establishing a tolerance of 25 ppm for inorganic bromide residues, resulting from soil application of EDB, found in or on peanuts.

4/13/66 Joint USDA-HEW statement for implementation of NAS/NRC recommendation published in the Federal Register. Plan included discontinuation by 12/31/67 of registrations involving residues on food or feed for which a tolerance or exemption was lacking. However, extensions were granted until December 31, 1970, if progress was being made to support the conclusion that the registration could be continued without undue hazard to the public health.

6/29/66 Due to lack of toxicity data, USDA withdrew petition for inorganic bromide residue tolerance increase on Mexican oranges.

1/30/68 PR Notice (68-5) published extending EDB "no residue" and "zero tolerance" registrations until 1/1/69 for use on apples, apricots, dry beans, beets, cabbage, celery, cucurbits, olives, peaches, pears, peas (dry), seed beds, spinach and turnips (per uses listed on pages 400, 401, 403,404, 404 of USDA Summary of Registered Agricultural Pesticide Chemical Uses).

2/1/68	PR Notice (68-6) published cancelling EDB "no residue" and "zero tolerance" registrations for use on alfalfa, mushrooms, peas, soybeans, sugar beets, general fruit and vegetable uses and nuts (per uses listed on pages 400, 402-405, USDA Summary).
4/24/68	PR Notice (68-8) published classifying fruit tree soil fumigation and honey comb fumigation as non-food uses (per uses listed on pages 401, 405, USDA Summary).
1/10/69	PR Notice (69-1) published extending EDB "no residue" and "zero tolerance" registrations until 1/1/70 for uses as a soil fumigant on string beans, beets, cabbage, celery, corn (grain) cucurbits, seed beds, spinach and turnips (per uses listed on pages 400, 401, 403, USDA Summary) and as a commodity fumigant on dry beans and dry peas (per uses listed on pages 404, 406, USDA Summary).
9/19/69	USDA petitioned FDA for the establishment of a tolerance of 10 ppm for inorganic bromide residues, resulting from post harvest application of EDB, found in or on longan fruits.
9/23/70	Federal Register notice published estab lishing tolerance of 10 ppm for inorganic bromide residues, resulting from post harvest application of EDB, found in or on longan fruits.
2/26/70	PR Notice (70-4) published cancelling EDB uses previously extended by PR Notice (69-1), with the exception of cucurbits, due to lack of reponse for finite tolerances (or exemptions) and lack of progress of safety investigation.

4/16/73 Pesticide Petition submitted by Interregional Research Project No. 4, Rutgers University (on behalf of the IR-4 Technical Committee and the Agricultural Experiment Station of Pennsylvania) requesting either an exemption from tolerance for methyl bromide and EDB and their inorganic bromide residues when used as a post-harvest fumigant on comb honey or honey or a tolerance of 25 ppm for inorganic bromide residues found in or on comb honey or honey as a result of post-harvest fumigation with EDB.

11/23/73 IR-4 Petition denied by FDA as a result of insufficient toxicological data to safely support a tolerance of 25 ppm for residues of methyl bromide or EDB found in or on comb honey and honey and due to a 9/4/73 letter from Dr. Weisburger of NCI stating that EDB produces " a high incidence of squamous cell carcinoma of the stomach" when administered at high doses during chronic feeding studies conducted rats and mice.

7/14/75 The Environmental Defense Fund petitioned EPA to investigate the carcinogenic potential of EDB pesticides and to either suspend or cancel their registrations. This request was reiterated on Jan. 21, 1976, and again on September 30, 1976. The Agency responded to these requests in March and October 1976 indicating that EDB pesticide registrations were being reviewed under the RPAR procedure.

8/26/77 The Environmental Defense Fund amended their earlier petition to include that EPA act under authority granted by the recently enacted Toxic Substances Control Act as well as under FIFRA.

C. Environmental Occurrence

1. Residues in Soils and Water

EDB does not degrade appreciably over a two week period (McHenry, 1972) but is converted almost completely to ethylene and bromide ions in about two months (Castro and Belser, 1968). Thomason, et al (1971) stated that EDB is "physically and/or biologically degradable."

Levels of EDB, in the nanogram per gram range (one billionth of a gram per gram), were found in soil at two citrus fumigation centers in Florida. EDB levels in dustfall at these centers ranged from 6 to 363 picograms (one trillionth of a gram) per square centimeter per hour. No detectable residues of EDB were found in either soil or dustfall at bulk gasoline handling facilities in New Jersey and Oklahoma. The minimum detectable quantity was 10-15 nanograms per sample (Going and Spigarelli, 1976).

Very low levels of EDB, less than 0.2 micrograms (millionth of a gram) per liter, were found in the aqueous effluent stream from one oil refinery; rainfall runoff water from the area of several retail gasoline stations also contained less than 0.2 micrograms per liter. Rainfall samples collected close to one of the fumigation centers had an EDB level of one microgram per liter and the runoff from this same center contained two micrograms per liter. The minimum detectable quantity was 10-15 nanograms per sample (Going and Spigarelli, 1976).

2. Residues in Air

In the Going and Spigarelli study, (1976), baseline air levels of EDB for rural/suburban areas and metropolitan areas were found to be 0.05-0.10 and 0.1-0.4 micrograms per cubic meter, respectively. Elevated air levels of EDB were found at the two citrus fumigation centers - up to 96 micrograms per cubic meter downwind of the centers, and up to 6,931 micrograms per

cubic meter in the breathing zones of persons in the buildings of these centers. The limit of detection was 10 parts per billion (ppb).

Atmospheric residues of EDB have recently been measured during an operational soil fumigation with this compound in three California locations. Table 2 presents the data from this study (White and McAllister, 1977).

3. Residues in Food and Feed

The literature on EDB residues in food and feed generally fall into two categories. The first category includes studies which were designed primarily to document the expected rapid loss of EDB residues, following fumigation, over short periods of less than one week. The

Table 2. Atmospheric residues during EDB soil fumigation by injection. Measurement 12" above ground and in applicator's breathing zone. (adapted from White and McAllister, 1977).

Application Rate lbs/acre	Duration of Sampling hrs.	Avg. Conc. Adjacent Untreated Field mg/M^3	Avg. Conc. Treated Field mg/M^3	Avg. Conc. Breathing Zone of Applicator mg/M^3	Amount a/ Inhaled mg/kg/d
135 b/	7.5	0.375	3.325	3.187	0.6
84.3 c/	7.0	0.075	0.712	4.850	1.0
31.5 d/	6.5	ND e/	———	0.500	0.1

a/ Assumptions - 70 kg man, breathing 1.8 M^3/hr/8 hr day, retains all inhaled EDB.
b/ Broadcast treatment, closed system, air inversion developed by mid-afternoon.
c/ Broadcast treatment, polydrum system, applicator left valve open while chisels were out of ground.
d/ Row treatment, polydrum system, sampling pump malfunctioned in treated field - no sample collected.
e/ Not detected.

analytical methodology in these studies was generally designed to measure either total bromides or inorganic bromide and was not sensitive to EDB levels below one ppm. The second category includes studies which were designed to measure EDB residues *per se* and which were usually carried out for periods of a week or more following fumigation. The following discussion of EDB residues is based on studies which fall into this second category.

Brown, *et al* (1958) and Beckman, *et al* (1967) showed large increases of inorganic bromine ion in crops grown in soils fumigated with EDB and other organic bromide compounds. Castro and Schmitt (1962) and Thomason, *et al* (1971) have shown that no detectable residues of organic EDB are found in plants grown in EDB-fumigated soils.

Caylor and Laurent (1969) reported commercially fumigated oats used as chicken feed were found to have residues of 10-15 ppm (mg/kg) several weeks after fumigation.

In a series of studies, a group of Israeli scientists measured residues of EDB in the peel and pulp of grapefruit, oranges, and lemons (Chalutz, *et al*, 1971; Chalutz, *et al*, 1972; Alumot and Chalutz, 1972; Bussel and Kamburov, 1976). These authors used a GLC method based on one developed by Bielorai and Alumot (1965) for EDB analysis on fumigated grains. With this method, residues of 1-43 ppm were found in the peel, and 0.4-2.4 ppm in the pulp at four days postfumigation. Residue levels were dependant on the rate and length of fumigation and the temperature and length of the post-fumigation aeration. Bussel and Kamburov (1976) showed that the residues in both peel and pulp dissipated completely in less than two weeks.

Dumas (1973) and Dumas and Bond (1975) reported on the levels of residues in apple skin, pulp and seeds following EDB fumigation at several rates and temperatures. Initially high residues of up to 308 ppm decreased to <0.1 ppm in 4 weeks, except seeds which retained levels of 25 ppm up to 13 weeks (note: this is not a registered use in the U.S.).

Wit, *et al* (1969) measured EDB residues resulting from experimental 10-day fumigation of wheat at a calculated rate of 1.41 l/metric ton. Using an analytical method sensitive to 0.001 ppm these authors reported residues of 5-30 ppm in the whole wheat which resulted in 2-4 ppm in the flour milled from this wheat, and 18-23 ppm in the "shorts" and bran. White bread baked from the flour showed EDB residues of 0.002-0.04 ppm while whole meal bread, baked from flour containing about 25% shorts and bran combined, showed residues of 0.006-0.026 ppm. The higher values were found in the wheat that had been aerated post-fumigation for 2-4 weeks while the lowest values were found in wheat aerated for 10-12 weeks.

In a study related to development of analytical methods, McMahon (1971) analyzed wheat and milo which had been commercially fumigated with a mixture of 6.6% EDB, 70.5% carbon tetrachloride, 16.5 % carbon disulfide and 6.4% methylene chloride at a rate of one gallon/1000 bushels of grain. Using a method with a sensitivity of 0.3 ppm, this author reported EDB residues of 2.5-6.1 ppm in the wheat samples and 1.3 ppm in the single milo sample. Analysis was carried out 3 weeks to 2 months following fumigation of the wheat and 3 months, post-fumigation, for the milo. The highest levels in the wheat were found in the samples with the shortest post-fumigation period.

In a study of commercially fumigated wheat, Berck (1974), using a fumigation rate of one half that used by Wit *et al* (1969) found EDB residues in the fumigated wheat and in flour milled from this wheat but not in bread baked from this flour. The fumigant mixture, contained 63% carbon tetrachloride, 30% ethylene dichloride, and 7% EDB and was applied at a rate of 0.67 l/metric ton. With a method sensitive to 0.01 ppm, this author reported EDB residues in the wheat ranging from 3.26 ppm at one week post-fumigation to 1.36 ppm at seven weeks post-fumigation. EDB residues in flour from this wheat ranged from 0.29 to 0.01 ppm; bran ranged from 0.40 to zero ppm; and middlings ranged from 0.30 to zero

ppm. In contrast to the findings of Wit, et al (1969), no EDB residues were found in 72 subsamples from 24 loaves of bread baked from the fumigated wheat.

In partial explanation of the wide ranges of residues reported following fumigation of citrus fruits and other raw agricultural commodities, Coggiola and Huelin (1964) reported that "appreciable quantities" of EDB were absorbed by wood, rubber, petroleum grease, concrete, and certain paints and plastics associated with fumigation chambers or packing materials.

Unpublished data obtained by Litton Bionetics, Inc. for Great Lakes Chemical Corporation indicated no detectable residues of EDB from the pre-plant fumigation of soils for green beans, snap beans, lima beans, cucumbers, bell peppers, tomatoes, peas, eggplant, sweet corn, watermelons, okra, squash, peanuts, soybeans, potatoes, cabbage, and onions. Soybean hay showed apparent residues corresponding to EDB of 0.09, 0.08, and 0.02 ppm (Litton Bionetics, 1977). The method of analysis, as reported by Litton Bionetics (1976), was able to detect as little as 0.4-0.5 nanograms per sample with a limit of sensitivity of 0.010 ppm (mg/kg).

4. Metabolism

The following discussion is adapted from the EDB criteria document (NIOSH, 1977) and references therein unless otherwise noted.

Under sterile conditions EDB can be very persistent. For example, its half-life in water (pH 7) at 20°C is 14 years. Like other halogenated alkanes, EDB is reactive toward a broad class of chemicals - nucleophiles - through the process of alkylation. In fact, it is this reaction of EDB with one of these nucleophiles, glutathion, which provides a major detoxification route in higher organisms (Nachtomi, 1970, Nachtomi, et al, 1966) althrough enzymatically catalyzed degradation reactions also assist in the elimination of EDB from

organisms. A measure of the speed of these processes is shown by the reported halflives of EDB in intravenously injected rats and chicks, of less than two hours and less than 12 hours respectively.

While its electrophilic behavior in the presence of nucleophiles assists in detoxifying an organism, this same ability to enter into alkylation reactions has been linked to a mechanism for damaging DNA. Specifically, alkylating agents such as EDB can also react with nucleophilic groups which are an integral part of DNA. The reaction product is a DNA molecule which has been altered by the addition of a covalently bonded alkyl group. This ability to alkylate DNA is shared with a number of chemicals which have been shown to be carcinogenic and/or mutagenic (Fishbein, 1976).

The presence of two bromine atoms on different carbon atoms admits the possibility of EDB entering into two separate alkylation reactions. The initial monoalkylation product between EDB and a substrate (e.g. DNA) heteroatom, such as nitrogen, oxygen, or sulfur, is a "half-mustard" reagent which could spontaneously cyclize through the other carbon atom to form a strained three-membered ring. This highly reactive intermediate may then undergo a second alkylation reaction with cellular DNA resulting in a covalent link between the DNA strands which may interfere with normal separation of the strands during DNA synthesis and subsequent cell division. Because of this additional reactive capability such bifunctional alkylating agents tend to possess a considerably greater biological activity than monofunctional agents of the same primary reactivity.

These alkylating agents may also alter the chemical behavior and physical characteristics of cellular constituents so as to prevent the altered molecules from functioning normally in physiological processes. This may account, in part, for the subsequent deleterious effects observed in biological systems exposed to EDB. Note also that when the risk of induction of

II. SUMMARY OF EVIDENCE TO SUPPORT REBUTTABLE PRESUMPTION

A. Chronic Effects

1. Oncogenicity

40 CFR 162.11 (a)(3)(ii)(A) provides that a "...rebuttable presumption shall arise if a pesticide's ingredient(s) . . . induces oncogenic effects in experimental mammalian species or in man as a result of oral, inhalation, or dermal exposure . . ." Section 162.3(bb) defines the term oncogenic as "the property of a substance or a mixture of substances to produce or induce benign or malignant tumor formation in living animals." The following study has been examined by the Working Group and found to present evidence which meets the above criterion.

a. NCI Bioassay on Rats and Mice

A National Cancer Institute (NCI) study was conducted at Hazelton Laboratories on Osborne-Mendel rats and (C57BL x C3H) F-1 mice between 1972 and 1974. Two dose levels, 80 and 40 mg/kg/day for rats and 120 and 60 mg/kg/day for mice, were initially selected. Fifty males and 50 females of each species were placed in these treatment groups, while 20 animals of each sex were used in the control (untreated) group. EDB was administered by intubation into the stomach daily, five days per week. Results obtained at various stages in the study have been reported in three published documents (Olson, et al, 1973; Ward and Habermann, 1974; Powers, et al, 1975) and in one unpublished report (Weisburger, 1977).

Olson, et al (1973) reported preliminary findings after the rats had been on dosage for up to 54 weeks and the mice for up to 42 weeks. Both a female and a male rat killed at the tenth week had a squamous-cell carcinoma in the stomach and, as the experiment progressed, this type of tumor was found in other rats that died or were killed because of ill health. By the 54th week 80 male rats, and 38 female rats,

on both high and low doses, had developed this type of tumor; none of the control animals had tumors of this type while only one female control rat had developed a mammary adenoma. The corresponding numbers for mice was 4 males and 3 females, with no tumors in any of the controls.

The pathologists' report (Ward and Habermann, 1974) for this study cited the results of their examination of the male rats, used in the low dose exposure, as similar for all groups of both species. They found diffuse squamous-cell hyperplasia (acanthosis and hyperkeratosis) of the forestomach with many papillomatous projections. They further reported metastases to the peritoneal cavity, mesotheliomas, poorly differentiated stomach tumors, intestinal tumors, and nodular hyperplasia in the liver. They concluded that EDB was "very carcinogenic."

Powers, et al, (1975) reported the findings ". . . at termination of these studies following 62nd week of treatment with EDB ...", (the actual time on treatment for each species versus the time to termination of the study is not clearly identified in this or the other three reports). Powers et al, reported the incidence of squamous-cell carcinoma of the stomach in excess of 90% for rats and 70% mice.

In a draft report presented at a National Cancer Institute seminar, Weisburger reported the findings of this same study in more detail (Weisburger, 1977). The total incidence of squamous-cell carcinomas, metastases and other tumors was tabulated in this report but no information was presented on the actual time frame involved. Table 3 presents a summary of Weisburger's data on stomach tumors in both rats and mice.

b. Interpretation of NCI Study

The recently completed criteria document on EDB (NIOSH, 1977) stated "The irregularities in the dose regimens of both species, the use of the suggested maximum tolerated dose,

and the route of administration do not negate the importance of the fact that ethylene dibromide has induced carcinomas in two mammalian species. The data from this single study indicate that ethylene dibromide is a carcinogen after daily introduction of about one-half the maximum tolerated dose into the stomach of rats and mice for up to 62 weeks."

Table 3 - Incidence of stomach tumors in rats and mice induced by intubation of EDB (adapted from Weisburger, 1977).

Species & Sex	High Dose[a/]	Low Dose[a/]	Control[a/]
Rat, female	30/31 (96.8)	41/42 (97.6)	1/10 (10.0)[b/]
Rat, male	35/41 (85.4)	49/50 (98.0)	0/20 (0)
Mouse, female	29/50 (58.0)	48/49 (98.0)	0/20 (0)
Mouse, male	31/49 (63.3)	45/49 (91.8)	2/19 (10.5)

a/ upper figure = number with tumor; lower figure = number examined; figure ( ) = percent with tumors

b/ Final tabulation of pathology data was not completed at time of this draft table (E.W.)-actual numbers of specific tumor types may differ from these numbers.

The International Agency for Research on Cancer (IARC) included an evaluation of the carcinogenic risk to man for EDB in its recently issued monograph (IARC, 1977). The comment of the IARC Working Group on the NCI study was as follows: "[EDB] is carcinogenic in mice and rats after its oral administration, the only route tested; it produced squamous-cell carcinomas of the forestomach."

The Carcinogen Assessment Group (CAG) of EPA has provided a preliminary statement regarding the results of the NCI/Hazelton study (EPA, CAG Memo, 8/26/77). They concluded with the following comment: "In the NCI investigation (Hazelton Laboratories, Contractor), rats

and mice were exposed to EDB for two years by intubation. A final report from NCI is not available to the Agency, but the final data compilations have been received (8/10/77). From our quick review of the data compilation tables and a manuscript by Elizabeth K. Weisburger (NCI)[1/], we can state that EDB causes a significant increase in the incidence of gastric carcinomas in both sexes of rats and mice. Metastases of these tumors are reported. The tumor rates appear to be high, and the differences are highly significant."

2. Mutagenicity

40 CFR 162.11(a)(3)(ii)(A) provides that a ". . . rebuttable presumption shall arise if a pesticide's ingredient(s) . . . induces mutagenic effects as determined by multitest evidence." Section 162.3 (4) defines the term mutagenic as ". . . the property of a substance or mixture of substances to induce changes in the genetic complement of either somatic or germinal tissue in subsequent generations."

Numerous studies report on various aspects of the mutagenic potential of EDB. The following studies have been examined by the Working Group and found to present evidence which meets the above criterion.

The following discussion is based in part on a review performed for EPA's Office of Toxic Substances in 1976 by the SRI (1977), as well as reviews performed by EPA's CED. The cited reports have been organized as to whether they show positive or negative effects[2/]. Under each

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1/ The final tabulation of pathology data was not completed by NCI at time of Weisburger's draft (1977). Since then the CAG has received the final data compilations of the histopathology findings and is presently reviewing them and a supplemental report will be made available at a later date.

2/ studies with insufficient data for evaluation of the claimed effects are categorized as negative.

of these categories, the studies have further been organized according to the resulting genetic end effects, i.e. point (gene) mutation (1); chromosomal damage (2); and primary DNA damage (3).

a. Positive Effects

(1) Point (gene) mutation studies

Buselmaier, et al,-1972

EDB was shown to cause reversions to histidine prototrophy in Salmonella typhimurium G-46 in the host-mediated assay in mice. In this test a single high dose of 500 mg/kg was administered intramuscularly to the mice and the bacteria were incubated in the peritoneal cavity. The mutation frequency was 6.23 loci/10^8 cells in the treated animals and was 0.77 loci/10^8 cells in untreated controls.

Because of the high mutation frequency relative to that of controls, the test is judged to be positive with the reservation that the activity was reported only for a single high dose, and there were no data presented to indicate a dose-response. As it was also reported to be active in vitro in a qualitative test, there is no evidence that mammalian metabolism in any way affects the mutagenicity of EDB for S. typhimurium G-46.

McCann, et al, 1974

EDB, administered as a liquid directly into molten agar containing the bacteria, has been shown to be "weakly active" in inducing reversions to histidine prototrophy in Salmonella typhimurium TA1535 and TA100. The activity was linearly dose-related, and the test was carried out without a mammalian metabolic activation system. There were 0.029 revertants per microgram. Since EDB is volatile, application into molten agar may not be the optimal mode of exposure. Dr. V.F. Simmon of the Stanford

Research Institute has stated that higher mutation frequencies are observed in Salmonella when EDB is placed on a filter disc and then laid on the agar, or when the plate containing the bacteria is exposed to the compound as a vapor (personal communication, cited in the SRI, 1977 study).

Brem, et al, 1974b

EDB has been shown to be active in inducing reversions to histidine prototrophy in Salmonella typhimurum strains TA1530 and TA1535, but not in TA1538. This indicates that EDB interacts with DNA to produce a base substitution. In these tests, 10 microliters of the chemical were applied to a filter paper disc, which was then laid on hardened agar containing the bacteria. Using the same technique for exposing the bacteria to EDB, a linear, dose-related increase in mutagenic activity over a range of approximately 2-12 micromoles/plate was observed in strain TA1530. Since this exposure technique does not completely accommodate the volatility of EDB, it is probable that mutation frequencies observed (e.g., 300-1500 revertants/plate over the dose range tested in strain TA1530) may be lower than could have been expected had the bacteria been exposed to the full dose of the chemical.

Malling, 1969; De Serres and Malling, 1970

EDB has been shown to cause forward mutations to a requirement for adenine in Neurospora crassa at the ad-3 gene locus. The conidia were treated for 3 hours with 1.2-1.63 microliters/ml EDB in 0.06M phosphate buffer, pH 7.0, containing 10% dimethyl sulfoxide. At 1.6 microliter/ml the mutation frequency induced by the compound was 30 per 10^6 survivors compared to 0.5 per 10^6 survivors for untreated controls.

Vogel and Chandler, 1974

EDB was reported to be active in the induction of sex-linked recessive lethal mutations in Drosophila melanogaster. Males were given an

0.3 mM solution of the chemical orally over a three-day period, and then mated with sets of two new females every three days to establish three broods. Although the results of only one dose level are reported, a significant increase in percent of lethal mutations over controls was observed, particularly in the second and third broods, which corresponds to effects on the spermatid and spermatocyte stages of spermatogenesis.

Clive, 1973

Clive tested the mutagenic po ential of EDB on the mouse lymphoma L5178Y cell culture system. EDB concentrations of 0.0-3.0 mM were used with 2-hour exposure times. The induced mutagenic frequency ($3X10^{-4}$ mutants per cell at a concentration of 0.001 moles of EDB for 2 hours) was dose-related and approximately equivalent to a dose of 650 R of X-irradiation.

Sparrow and Schairer, 1974; Sparrow et al, 1974; Nauman, et al, 1976

This group of scientists at the Brookhaven National Laboratory have reported that EDB caused pink somatic mutations in stamen hair cells of Tradescantia mutable clones 02, 0106, and 4430. Sparrow and Schairer (1974) concluded that gaseous concentrations of less than 10 ppm EDB for six hours significantly increased the mutation rate in this plant system and that the relative effectiveness of various mutagens can be estimated, and may be indicative of their hazard to man. Sparrow, et al, (1974) determined the dose-response curves for EDB and compared this with X-ray dose-response curves using clones 02 and 4430. These authors concluded that the phenotypic changes resulting from these exposures (pink and colorless) may be associated with chromosome breakage, gene mutation, chromosome non-disjunction, or somatic crossing over.

Nauman, et al, (1976) concluded that intercomparisons among the exposure-response curves of X-rays, ethyl methanesulfonate and EDB, in this

test system, demonstrate that gaseous chemicals can be as, or more, mutagenic than X-rays. One clone (4430) showed a relatively low sensitivity to X-rays, but a consistently high sensitivity to the chemical mutagens tested.

Ehrenberg, et al, 1974

In a study to determine the relationship between reaction kinetics and mutagenic activity of methylating and beta-halogenoethylating gasoline additives, EDB was reported to be mutagenic in barley kernels.

(2) Chromosomal Damage studies

No positive chromosomal damage studies have been found for EDB.

(3) Primary DNA damage studies

Meneghini, 1974

EDB, at dosages covering the range of 10^{-6}- 10^{-2}M/ 15 x 10^{6} cells, was found to induce unscheduled DNA synthesis (UDS) in opossum lymphocytes treated for one hour. This is evidence that the test compound is interacting with DNA. The effect observed was dose-related and the level of UDS was greater than that induced by either methyl- or ethyl- methanesulfonate*, known potent gene and chromosomal mutagens in mammals.

Fahrig, 1974

EDB was reported to be highly active in inducing mitotic gene conversion in Saccharomyces cerevisiae D_4 at the adenine 2 and trytophan 5 loci. The effect reported was strongly positive. At a concentration of 0.17 mM on treatment for

* These two compounds are generally used as positive controls in mutagenic studies.

27 hours, 10.8 convertants per 10^5 survivors were observed at the ade$_5$ locus vs. 0.48 per 10^5 survivors in untreated controls. At the trp$_5$ locus, 8.85 convertants per 10^5 survivors were observed vs. 0.82 per 10^5 survivors in untreated controls.

b. Negative Effects

(1) Point (gene) mutation studies

Alper and Ames, 1975

EDB has been shown to be inactive in inducing deletions in the gal-chlA gene region of Salmonella typhimurium LT-2.

Buselmaier, et al, 1972

EDB, administered intramuscularly, was reported to be inactive in inducing reversions to leucine prototrophy in Serratia marcescens A21 in the host-mediated assay in the mouse. The compound was also reported to be inactive in S. marcescens in a qualitative test in vitro. The data presented are insufficient for evaluating the effect of EDB in the host-mediated assay with S. marcescens, since results at only a single dose were reported.

Brem, et al, 1974b

EDB, tested at a single dose of 10 microliters was reported to be inactive in the Salmonella typhimurium TA 1538 strain using the filter paper disc technique. Because data for only a single dose were reported and because of the inaccuracy inherent in determining the effective dose by the filter paper technique, this result is insufficient for evaluating the mutagenicity of EDB in strain TA1538. However, such inactivity in strain TA1538 might be predicted since the strain is designed to detect frame-shift mutagens and EDB is more ikely to cause base-substitution mutations.

(2) Chromosomal damage studies

Two types of tests related to chromosomal effects have been reported as negative. These are the dominant-lethal (DL) test in mice, and *in vitro* cytogenetic tests. The DL test is an insensitive test and the *in vitro* cytogenetic tests are difficult to perform and evaluate due to cellular toxicity effects.

Epstein, *et al*, 1972

EDB was reported to be inactive in inducing mutations when administered intraperitoneally (18 or 90 mg/kg) or orally (5 times, 50 or 100 mg/kg) to male ICR/Ha Swiss mice. This report is essentially a review article and the data presented were insufficient for establishing a negative result, primarily because none of the relevant parameters were tabulated (e.g. total implants, early fetal deaths, and pregnancy rates).

Kristoffersson, 1974

EDB was reported to be inactive in inducing chromosome breakage in human lymphocytes and onion root tips. This report was a meeting abstract and no data were presented on which to base an evaluation.

(3) Primary DNA damage studies

Brem, *et al*, 1974a & 1974b

EDB has been reported to be more toxic to DNA repair deficient *Escherichia coli* P3478 (pol A-) than to repair competent *E. coli* W3110 (pol A+). Greater toxicity to strain P3478 may reflect potential for inducing DNA damage. The data reported are insufficient for evaluating the effect of the chemical since results at only a single dose (10 microliters per plate) are presented.

c. Interpretation of Mutagenicity studies

The NIOSH criteria document concludes that the mutagenic potential of EDB has been established in a wide spectrum of mutational test systems

for point (gene) mutations typical of the activity of an alkylating agent which forms covalent bonds with DNA (NIOSH, 1977).

In a memorandum, dated 9/10/77, Dr. R. Pertel stated that there is ample evidence to fulfill both the multitest criteria for EDB as a mutagen as well as the scientific criteria of the EPA Science Advisory Board's (SAB) study group on mutagenicity. This evidence shows EDB to be positive in both prokaryotic (microbial) and eukaryotic (higher forms including mammals) for point (gene) mutational effects, with and without mammalian metabolic activation.

3. Other Chronic Effects--Reproductive Effects:

40 CFR 162.11(a)(3)(ii)(B) provides that a "... rebuttable presumption shall arise if a pesticide's ingredient(s), metabolite(s), or degradation product(s) ... produces any other chronic or delayed toxic effect in test animals at any dosage up to a level, as determined by the Administrator, which is substantially higher than that to which humans can reasonably be anticipated to be exposed, taking into account ample margins of safety."

The Working Group has examined the following reproductive effects studies and finds them to present evidence which meets the above criterion. The Working Group also finds that, because sufficient data do not exist for determining a "no-observable-effect" level for the reproductive effects of EDB via oral, inhalation or dermal routes of exposure, acceptable levels of exposure may not be calculated for persons exposed by any of these routes following the pesticide uses of EDB. Furthermore the Working Group believes that the difference between the levels of EDB to which bulls were exposed and at which reproductive effects were evidenced (avg. dose of 2 mg/kg/day - see Table 4), and the levels to which field applicators and citrus fumigators may be exposed (0.1 - 1.0 mg/kg/day - see Table 2, and up to 0.425 mg/kg/day - see Table 3, respectively), does not constitute an ample margin of safety. Therefore a rebuttable presumption exists under this criterion for all pesticide products containing EDB.

Studies on bulls, cows, sheep, and rodents establish that EDB may adversely affect mammalian development by interfering with the production of male gametes and with the development of embryos. These studies are summarized below. Following those summarizations, data on levels to which humans can be exposed are presented.

a. Animal Studies

(1) Bulls

Several studies by Israeli scientists have established that oral exposure of EDB to bulls is associated with reduced sperm production, reduced sperm motility, and abnormal sperm structure. These studies are summarized in Table 4 and some examples of the results are presented below.

Amir and coworkers described the effects of EDB on sperm in a series of experiments in which EDB was administered to bull calves (starting at 4 days of age) or adult bulls at an average dose of 2 mg/kg/day for periods up to 24 months. The general protocol involved the administration of a 4 mg/kg dose on alternate days by capsule, with variation from this protocol for the calves under 12 months of age. At various periods following the beginning of treatment, and after age 14-16 months for calves, sperm samples were examined either in the testes or in ejaculates.

For example, Amir (1973) reported that the testis of a bull examined after receiving seven doses over 12 days contained 50% sperm with misshapen heads in the testis and 10% in the caput epididymus. The sperm of another bull examined after 10 doses over a 21 day period had approximately 90% misshapen heads in both the testis and caput epididymus. No data were presented on the occurrence of misshapened sperm in comparable untreated animals.

Table 4 - Summary of reproductive effects of EDB in bulls.

Route of Exposure	Sex and Age	EDB Conc, and Duration	Observed Effects	Reference
Oral milk 3 mo. feed 9 mo. capsule over 12 mo.	three bull calves	4 mg/kg/d on alternate days 4d - 24 mo.	no effect on growth or libido, abnormal spermatozoa, decreased sperm density and motility, recovery 10 d-3.5 mo. in 2 animals after discontinued, recurrence of above after renewal of treatment.	Amir and Volcani, 1965
Oral same as above	same three calves as above	same dose and duration as above, unilaterally castrated at 17 1/2 - 22 1/2 mo.	testes at castration, depopulated of spermatozoa, showed histologic changes, semen from remaining testis in two animals normal 3-4 mo. after discontinued, decreased sperm density and motility in third animal.	Amir and Volcani, 1967
Oral capsule	two bulls 15-20 mo.	4 mg/kg on alternate days 12 d & 21 d	abnormal spermatozoa in testes, epididymis, ductus deferens, and in ejaculate.	Amir, 1973
Testicular injection or oral capsule, labeled EDB	four bulls 15-20 mo.	one bull injected one-120 mg dose; one bull each 10 oral doses 2 gm, 220 mg, 350 mg	abnormalities of spermatozoa remained maximal while radioactivity of seminal fluid and spermatozoa declide to low levels, EDB affected spermiogenesis and sperm maturation	"

Table 4 (Continued) - Summary of reproductive effects of EDB in bulls.

Oral capsule	three bulls 15-20 mo.	4 mg/kg/d on alternate days 10 doses	high percentage of sperm abnormalities 12-17 d after start, % abnormalities decreased about 1 mo. following cessation of treatment, decrease of sperm motility but not density, (see Amir and Volcani, 1966.)	Amir and Ben-David, 1973
Injection olive oil in testes	two bulls 15-20 mo.	110-120 mg each one time	same as above, but no effect on sperm motility.	"
Oral capsule	same 3 bulls as Amir and Volcani, 1965 and 1967	4 mg/kg/d on alternate days 4d-24 mo.	see comments in Amir and Volcani, 1965 & 1967, bromine content of testis bull at slaughter-32 ppm [19 ppm control], semen Br content 23 ppm while on EDB decreased to control level of 7 ppm six mo. after discontinuation, all bulls showed histologic changes.	Bondi and Alumot, 1967
Oral capsule	three bulls 2 1/2 yr. old	2 mg/kg/d each day, unstated duration	time for appearance of sperm abnormalities "considerably longer" than 4 mg/kg/d on alternate-day regimen and recovery was faster.	"
Oral capsule?	26 bull "calves" various ages	0, 0.5, 1.0 2.0, 3.0, 4.0 mg/kg/d. until deformed sperm were seen.	prolonged dosing at 2 mg/kg/d, or higher doses of 3-4 mg/kg/d for short time periods, produced reversible changes in sperm morphology and histology of testes, epididymus and seminal vesicles; Br content at doses of 3-4 mg/kg/d increased to 50 ppm over 20 ppm for controls, no effect was demonstrated at 0.5 & 1.0 mg/kg/d.	"

Table 4 (Continued) - Summary of reproductive effects of EDB in bulls

Oral EDB in mash	three bull calves age unstated	50-60 ppm EDB 3 mo.	no effect on semen, no increase Br. content of testes.	Bondi and Alumot, 1967
Oral KBr in solution in mash	"	Br. equiv. to 2 mg EDB, daily 9 mo,	same as above	"
Oral capsule ?	four bulls age unstated	2 mg/kg/d duration unstated	no effect on fructose or citric acid in seminal plasma between treated or control animals.	"
Oral capsule	nineteen bulls 15-24 mo. old	4 mg/kg/d on alternate days 10 doses	abnormalities reached maximum 2-10 days post-treatment, effect was reversed 4-5 wks post treatment.	Amir, 1975
"	2 adult bulls	"	abnormalities reached maximum within one week post treatment, reversed incompletely at 16 wk. post treatment.	"
Oral capsule	seven bulls 15-18 mo. old	4 mg/kg/d on alternate days	no significant changes in total nitrogen, amino acid, or lipo - protein content of spermatozoa 1-13 days post treatment, significant changes in amino acid in sperm proteins and lipoproteins.	Amir and Lavon, 1976
"	three bulls 4 1/2 - 5 1/2 yr. old	"	same as above.	"

In a similar study on sperm morphology Amir and Lavon (1976) examined sperm on the day following the last EDB dose (4 mg/kg on alternate days for 20 days) in four young bulls. Sperm morphology in three of the bulls was similar to the control value of 4% and 9% misshapen heads in the caput and cauda epididymus respectively. Seventy percent of the fourth animal's sperm were misshapen in the caput epididymus and 15% were misshapen in the cauda epididymus. Three older bulls contained 100% misshapen sperm in their ejaculates 6-9 days after beginning treatment and, in 9-13 days most of the sperm cells were degenerating. No control values were presented for the older bulls. The dry weight of the sperm in the caput epididymus showed a two-fold reduction from 3340 $\pm$ 107 micrograms/10^8 sperm before treatment to 1494 $\pm$ 137 micrograms/10^8 sperm after treatment. Sperm in the cauda epididymus showed no change in dry weight while a slight reduction, from 1854 $\pm$ 128 micrograms/10^8 sperm to 1419 $\pm$ 60 micrograms/10^8 sperm was apparent in the ejaculates.

In a study of EDB effects on sperm motility, Amir and Ben-David (1973) reported marked decreases in motility and increased frequency of structural defects in bull sperm following treatment (4 mg/kg in 10 doses on alternate days). The ejaculates of three bulls contained 42%, 50% and 65% motile sperm before exposure to EDB while approximately 30 days after treatment ejaculates from these same bulls contained 5%, 4%, and 3% motile sperm, respectively. Corresponding changes in sperm morphology were also reported: before treatment ejaculates contained 4-17% abnormal sperm, while approximately 30 days after treatment ejaculates from these animals contained 88-100% abnormal sperm (Table 5).

In another sperm motility study, Amir (1975) reported marked decreases in sperm concentration for two adult bulls after EDB treatment. During the first two weeks of treatment the

Table 5 - Sperm characteristics and motility in bulls treated orally with ten doses of EDB (4 mg/kg body weight/dose) on alternate days (from Amir and Ben-David, 1973)

Days After Start of Treatment	Number of Sperm Collections	% Abnormal Spermatozoa (Range)	% Abnormalities			Sperm Motility (% Motile Cells) Mean ± SE
			Tail and Acrosome Defects	Misshapen Heads Pear-shaped	Degenerating	
Bull No. 98						
Pre-treatment	4	4-9	90	8	2	65 ± 2.9
0-14	7	3-14	90	7	3	66 ± 1.7
16-21	3	25-98	96	3	1	25 ± 17.6
23-39	7	90-100	11	7	82	3 ± 4.8
42-53	4	13-57	63	7	30	55 ± 8.7
64-75	4	9-14	88	7	5	65 ± 2.9
Bull No. 573						
Pre-treatment	4	7-10	89	8	3	50 ± 8.9
7-11	3	9-11	89	8	3	47 ± 6.0
14-16	2	67-79	96	3	4	3 ± 0.0
20-35	5	88-98	7	0	93	4 ± 1.9
39-53	4	14-87	35	57	8	42 ± 7.8
57-64	3	9-12	68	27	5	57 ± 7.5
Bull No. 879						
Pre-treatment	4	5-17	83	13	4	42 ± 11.6
0-45	7	6-12	85	12	3	41 ± 6.3
17-21	3	77-85	95	3	2	9 ± 5.3
25-35	5	100	3	42	55	5 ± 3.7
38-52	5	14-72	56	39	5	53 ± 2.0
56-61	3	6-10	81	15	4	47 ± 1.7

sperm concentrations for these bulls were 1330 and 1360 x 10^6 sperm cells/ml. One to two months after the start of treatment, these values had decreased to 6 and 9 x 10^6 sperm cells/ml. Sperm motility decreased from 72% and 45% early in treatment to no motile sperm one to two months after treatment. Five young bulls, also examined in this study, showed little effect on sperm concentration, but sperm motility decreased from 46% early in treatment to 8% 17-35 days after the start of treatment (Table 6).

Table 6. Sperm concentration and motility in ejaculates of bulls after oral treatment with EDB (adapted from Amir, 1975).

Test animal(s)	Days after Start of Treatment	Number of Ejaculates	Sperm Conc. (X 10^6 /ml) 1/	Motile Sperm % 1/
5	0-16	34	895 ± 58	46 ± 3.4
young	17-35	37	756 ± 51	8 ± 1.5
Bulls	36-67	35	810 ± 57	44 ± 3.3
Adult	0-15	5	1360 ± 103	45 ± 8.7
Bull	18-29	4	725 ± 66	0
#240	32-46	5	9 ± 5.6	0
	52-121	13	416 ± 66	22 ± 3.6
	126-141	3	967 ± 109	57 ± 3.4
Adult	0-15	6	1330 ± 11	72 ± 1.7
Bull	16-27	4	667 ± 100	17 ± 11.8
#251	32-63	9	6 ± 4.3	0
	67-131	16	9 ± 1.9	15 ± 3.8
	162-172	2	350 ± 50	5

1/ Values are means ± standard error of the mean

(2) Cows and Sheep

Limited data on cows, ewes, and rams were presented by Amir and Ben-David (1973), and Bondi and Alumot (1967). These investigators

reported no apparent effect on fertility or reproduction in the female animals or in two adult rams. These data are summarized in Table 7.

(3) Rats and Mice

Several studies of EDB exposure by IP, oral, or inhalation routes, have shown only limited and temporary reproductive effects in rats. The studies are summarized in Table 8. One study (Edwards, et al, 1970) showed a "transient" antifertility effect, through the spermatid stage of spermiogenesis, in male rats injected with five daily doses of 10 mg/kg body wt. Three Israeli reports indicated that high dietary doses of up to 30% of the LD have no effect comparable to those in bulls (Alumot, 1972; Amir and Ben-David, 1973; Bondi and Alumot, 1967).

In a study by Short, et al, (1976) pregnant rats and mice were exposed to EDB at airborne concentrations of 32 ppm for 23 hr/d from day 6 through 15 of gestation. Two other groups of rats and mice were used; one was the untreated control and the other was a restricted diet group. This dose of EDB was toxic to both rats and mice as evidenced by decreased food consumption and decreased weight gain. Body weight changes were also seen with the restricted diet group. Indices of fetotoxicity were seen to both rats and mice from EDB exposure, e.g., decreased implants per dam, decreased fetuses per dam, decreased fetal weight. Decreases in some of these same parameters were observed in the restricted diet group. Teratogenic effects were also seen and are discussed below under section IV.

(4) Chickens

Several studies have shown significant chronic effects on the reproductive system of chickens from ingestion of EDB. Toxic effects observed on hens include reduced egg production, reduced egg weight, reduced fertility , a generalized reduction in the permeability of ovarian mem-

Table 7 - Summary of reproductive effects of EDB in cows and sheep.

Route of Exposure	Sex and Age	EDB Conc. and Duration	Observed Effects	Reference
Oral capsule?	four mature cows	1200 mg/d (about 2 mg/kg/d) 2-3 mo. of pregnancy thru 3 lactation periods	no detrimental effect on fertility or reproduction.	Bondi and Alumot, 1967
Oral in milk for 1 week capsule thereafter?	four heifers 2nd mo of first pregnancy	1200 mg/d thru 3 lactation periods	possible effect on fertility though gestation and parturition appeared normal.	"
Oral?	six female calves	presumed to be 1200 mg/d, from birth to first parturition	no difference between controls and treated animals on fertility and reproduction.	"
Oral fumigated "concentrate"	three 6 mo.-old ewes	about 300 ppm in concentrate duration unstated	no apparent detrimental effects on reproductive ability.	Bondi and Alumot, 1967
Oral added to "concentrate"	"	"	"	"
Oral	two adult rams	unstated conc., 4 mo.	oral administration of unstated concentration "for more than 4 months, up to their death from acute poisoning;" no changes in spermatozoa in the ejaculates or in the epididymus (cited from Amir, 1969).	Amir and Ben-David 1973

Table 8 - Summary of reproductive effects of EDB in rats.

Route of Exposure	Sex and Age	EDB Conc. and Duration	Observed Effects	Reference
IP	Male rats number unspecified	10 mg/kg/d 5 doses	selectively damaged spermatogenic cells (spermatids) resulting in "transient" sterility as measured by avg. litter size of serially mated female rats, litter size reduced approx. 50% of controls at 3rd wk. post-treatment, to zero in 4th wk., returned to normal at the 5th-10th wks.	Edwards, et al, 1970
Oral "dietary"	male and female rats number unspecified	daily doses up to 100 mg/kg body wt. (25-30% of LD50) unspecified	no effect on growth, sexual development, and reproductive activity, failed to decrease fertility (based on unpublished data and personal communication)	Alumot, 1972 and Amir and Ben-David 1973
Oral fumigated mash	20 female rats 3 wks. old	100, 200 ppm in mash for appx. 8-16 mg/kg/d 12 wks.	when mated to untreated males, no effect shown on fertility, gestation or parturition including repeated gestations; retreatment following two gestations showed no effect on "breeding capacity" (fertility).	Bondi and Alumot, 1967
Inhalation	18 pregnant rats and 10 non-pregnant	32 ppm 23 hr/day from day 6-15 of gestation	decreased food consumption and wt. gin, decreased implants/dam, decreased fetuses/dam, decreased fetal wt., teratogenic effects-wavy ribs and hydrocephaly	Short et al 1976

branes and, at higher levels, a reduction in body weight. The most sensitive of these parameters appears to be egg weight. Table 9 summarizes the results of these studies.

In 1957 and 1958, commercial poultrymen in the Southeastern US encountered a decrease in egg production and egg size. A series of studies related to this problem showed that significant reductions in egg size and egg production were due to the level of EDB residues in the feed. Bierer and Vickers (1959) reported that grains fumigated with EDB and fed to laying hens, resulted in a gradual diminution in egg size and, in extreme cases, a complete cessation of egg production. The effect took eight weeks or longer to appear. Similar studies by Caylor and Laurent, (1960), and Fuller and Morris, (1962 and 1963) confirmed the findings of Bierer and Vickers in greater detail.

From their series of experiments, Alumot and coworkers concluded that prolonged feeding of mash containing EDB significantly depressed growth of male chickens when fed without restrictions, but that the depression seemed to result from reduced food intake and not from the direct action of the compound. They also concluded that EDB had no effect on the onset of egg production in hens fed from birth, on sexual development in males and females, and on sperm characteristics or fertility in mature males. Statistically significant reductions in egg size and egg fertility were noted in hens fed EDB-fumigated mash.

b. <u>Human Exposure</u>

Human exposure from registered pesticide uses of EDB may occur by several routes: during application as a soil or commodity fumigant, from residues in or on raw agricultural commodities, or in processed grain commodities following commercial fumigation.

Human exposure to EDB from soil fumigation applications has been calculated from unpublished data (White and McAllister, 1977) and

Table 9 - Summary of reproductive effects of EDB in chickens.

Route of Exposure	Sex and Age	EDB Conc. and Duration	Observed Effects	Reference
Oral fumigated grain & std. laying ration	laying hens	5-160 ppm 9 wks.	significant reduction in egg wt. and numbers (in 10-12 wks at 5-7.5 ppm), irreversible cessation egg laying within 46-56 d at 90 ppm.	Bondi, et al, 1955
Oral fumigated oats	laying hens	"normal" fumigation several mo. before 23 d	reduced egg size.	Bierer & Vickers, 1959
"	"	10X"normal" Dowfume ED-5 10d	marked reduction in egg size & number lasting 6 wks after return to clean rations.	"
Oral 50% fumigated oats 50% mash	12 m-old laying hens and "pullets"	unknown conc, 10 wks.	steady decline in egg size over 10 wks. for hens, no increase in egg size for pullets.	Taylor & Laurent, 1960
Oral fumigated oats	laying pullets	0.5-1.5 cc/lb (mixture EDB,EDC,CT) 119d	highly significant reduction in egg size (dose related), slow increase following removal to untreated feed, reversible decrease in egg numbers.	"
Oral fumigated corn	"	0.5 cc/lb above mixture 8 wks.	egg-size increase less than half of untreated controls.	"

Table 9 (Continued) - Summary of reproductive effects of EDB in chickens.

Oral solution directly into crops	laying pullets	EDB 0.5-20 mg/ hen/d (mixture of EDB,CT,&EDC) 8 wks.	no effect on egg production at or below 4.0 mg but significant effect at 8.0 mg,significant effect on egg wt, at 0.5 mg (lowest level tested), body wt. depressed slightly at max. dose, egg production and body wt, normal after 12 wks. clean diet, egg wt. below normal 6-10 months on clean diet; change in ovarian structure of affected birds.	Fuller & Morris, 1962
Oral fumigated oats	6 m-old laying hens	EDB 0.5,2.0,8.0 mg/ hen/d 12 wks.	significant reduction of egg wt. at 0.5 mg dose (5ppm), production reduced at 8.0 mg dose (80 ppm) only, no effect on feed consumption, body wt. or mortality.	Fuller & Morris, 1963
Oral directly into crops	"	0.5,1.0,2.0, 4.0,8.0 mg/ hen/d 12 wks.	same as above.	"
Oral feeding fumigated mash	3 d-old male cockerels	0,80,180 ppm regulated feeding to level of 180 ppm group 3 mo.	no observed effect on spermiogenic activity, spermatozoa count, or testes weight, comb wt. declined.	Alumot, et al, 1968
"	"	0,150,300 ppm unrestricted intake 12 mo.	at 150 ppm wt. gain reduced, at 300 ppm significant reduction in growth and feed intake, comb wt declined but no effect on body wt., testes wt., and semen.	"

Table 9 (Continued) - Summary of reproductive effects of EDB in chickens.

Oral fumigated mash	adult male	100 ppm 105 d,	no significant effect on semen, fertilization rate, or hatchability of fertilized eggs.	Alumot, et al, 1968
Oral fumigated mash	1 d-old female	0,40 ppm 2 X/d 3 mo.	significant decrease in egg wt., and egg production, normal onset of egg laying.	"
"	1 yr-old laying hens	0,100 ppm 4 wks.	significant reduction egg wt., and in fertilization rate, increase in number of dead embryos.	"
Oral in mash	Adult hens	0,10 mg/ Hen/d. 2-8 wks with various hormone treatments	treatment with various hormones had no effect on egg wt. reduction, EDB did not affect pituitary hormone production.	Alumot & Mandel, 1969
Oral in mash	laying hens	100 ppm until egg wt. had decreased to 2/3 of control	EDB reduced uptake of labled proteins but increased number of follicles per ovary.	Alumot & Harduf, 1971

is presented in Table 2. Using data presented in part in Table 2, the Criteria and Evaluation Division has made a preliminary estimate that professional applicators, applying EDB for 30-40 days per year, would receive a total annual inhalation dose of 3-40 mg/kg and farmer-applicators, applying EDB for 7-10 days per year, would receive a total annual inhalation dose of 0.7-10 mg/kg/year (EPA, 1977).

Limited data from a citrus fumigation center in Florida (Going and Spigarelli, 1976) provides a preliminary estimate of exposure as shown in Table 10.

Table 10. Potential inhalation exposure at a citrus fumigation center (EPA, 1977).

Sample Location	ug/m^3 EDB[a/]	Potential Inhalation Exposure[b/]
office	3100	0.425 mg/kg/day
corridor	376	0.052 "
exit driveway	0.73	0.001 "
1/8 mile south of site	29.3	0.004 "

a/ data from 13-hour average air sample

b/ Calculated by assuming a breathing rate of 1.2 m^3/hr for light activity, a body weight of 70 kg, an exposure duration of 8 hours per day for 250 days and complete retention of all inhaled EDB.

The only estimates, based on actual data, of residues in raw or processed commodities are calculated from the reports of Wit, et al, (1969) and Litton Bionetics (1977). The estimate based on the Wit, et al, paper, calculated from the highest residue in whole wheat bread reported in that study, is 0.00045 mg/kg/day. The previously cited data from the Litton Bionetics (1977) study on 15 vegetable crops provide an estimate of 0.00006 mg/kg/day when the minimum detectable level (0.01 ppm) of the methodology used in that study is assumed to be the actual residue.

NIOSH considers that the EDB occupational exposure limit should be substantially lower than the current Federal standard of 20 ppm as an 8-hour time-weighted-average limit with a 30 ppm ceiling. NIOSH has recommended that the occupational exposure limit for EDB be reduced to a ceiling concentration of 1.0 mg/M^3 (0.13 ppm) for any 15-minute sampling period. This is a decline of actual dose from 2212 mg/d (31.6 mg/kg/d) to 14.4 mg/d (0.21 mg/kg/d). This calculation of actual dosage assumes that the average 70 kg. human breathes 1.8 m^3/hr when moderately active and that all the inhaled EDB is retained. It is also assumed that 1 ppm EDB = 7.68 mg/m EDB and that a work day equals 8 hours. The NIOSH recommendation reduces by one two-hundred and thirtieth, the current federal ceiling for EDB (NIOSH, 1977).

III. SUMMARY OF EVIDENCE NOT SUFFICIENT TO SUPPORT AN RPAR

A. Acute Toxicity Criteria

1. Humans

Data presently available are insufficient to determine whether the risk criteria in 162.11(a)(3)(i)(A) are met or exceeded. Table 11 summarizes the published data of acute exposures to humans. Pesticide episode data (human exposure) presented below as well as exposure data presented in Tables 2 and 10, are also insufficient to determine whether these criteria are met or exceeded.

Data on acute toxicity of EDB to humans comes largely from observations of accidental exposures. The NIOSH criteria document (1977) cites four reports describing either accidental, industrial or experimental exposures. The pertinent observations from these reports are presented in Table 11.

In humans direct exposure to EDB causes irritation and injury to the skin and eyes. Exposure to the vapor has caused the development of respira-

Table 11 - Summary of effects of EDB exposure in humans (adapted from NIOSH, 1977).

Route of Exp.	Conc. & Duration	Observed Effects	Reference
respiratory (accidental)	70 g [a] single dose, during anesthesia	vomiting, abdominal pain, diarrhea, difficulty in breathing, restlessness, nervousness, dizziness, death by 44 hr. autopsy showed upper resp. tract irritating, swelling of pulmonary lymph glands, muscular degeneration of heart, liver and kidneys, hemorrhages in the trachea and along the mediastinum.	Marmetschke, 1910
"	Unknown repeated doses	irritation of conjunctiva, swelling of eyelids and glands under chin, skin sensitization	Kochmann, 1928
dermal	55% [b] several hr.	painful burning of feet with reddening and blisters between toes	Pflesser, 1928
"	0.5 ml [c] 30 min.	painful inflammation, swelling, and blistering of skin	"
"	0.5 ml [c] 10 min.	heat sensation, slight burning, painful swelling and reddening of skin for next 24 hr.	"
"	0.5 ml [c] 30 min.	swelling, reddening, and itching 30 min. later	"
oral (possible suicide)	4.5 ml single dose	vomiting, abdominal pain, diarrhea, nausea, anuria, death by 54 hr. autopsy showed lung edema and congestion, reddening of intestinal mucosa, massive centrilobular liver necrosis, damage to tubular epithelium of kidneys.	Olmstead 1960

a/ Unknown portion of 70 g dose actually inhaled.
b/ Unknown quantity mixed with gauge fluid.
c/ Skin washed with soap and water after exposure.

tory tract inflammation along with anorexia and headache with recovery after discontinuance of exposure. Von Oettingen (1958) reported weakness and rapid pulse associated with EDB exposure as well as cardiac failure resulting in death. Olmstead (1960) reported that an accidental ingestion of EDB caused liver necrosis and kidney tubular damage.

Accidental human exposures to pesticides are recorded voluntarily through the EPA Pesticide Episode Review System (PERS). A search of the PERS files covering the period 1966 - September 1976, identified 23 reports involving EDB as a pesticide, either alone or in combination with other chemicals (EPA, 1976). Of the 23 episodes, 16 reports cited 20 humans as the affected entities and the other seven listed environmental contamination as the only impact. Of the 20 humans involved, 8 were engaged in agriculture, 3 were at home (including 1 child), 2 were involved in "loading dock" accidents, and 1 each involved in commercial pest control, warehousing, a nut processing plant, an unspecified industry, and an unspecified job site. The most frequent symptom reported in these episodes was related to dermal contact and included erythema, dermatitis, blistering and chemical burns. Wheezing, chest pain and death were also reported.

2. Animals

The Working Group has not assessed whether the (acute) risk criteria, in 162.11(a)(3)(i)(A) or (B), to domestic animals, wildlife and aquatic species are met or exceeded. There do not appear to be sufficient data on this aspect and furthermore there appears to be little opportunity for EDB exposure to wildlife or aquatic organisms.

Data on the acute oral toxicity of EDB to various species of test animals is summarized in Table 12.

Table 12 - Acute oral toxicity of EDB to various test organisms.

Species	Sex or size	LD50 ppm	TLm[a] ppm (hr.)	Reference
Rats	M	146		Rowe et al, 1952
Rats	F	117		"
Mice	F	420		"
Rabbits	F	55		"
Guinea Pigs	Mixed	110		"
Chicks	Mixed	79		"
LM - Bass	Fingerlings		25 (24 hr)[b]	Davis and Hardcastle, 1959
"	"		15 (24 hr)[c]	"
"	"		15 (48 hr)[c]	"
Bluegill	"		25 (24 hr)[b]	"
"	"		18 (24 hr)[c]	"
"	"		18 (48 hr)[b]	"
Carp	5 cm		2.8 (48 hr)	Yoshida, 1972
Japanese Goldfish	4 cm		>40 (48 hr)	"
Killifish	2.5 cm		>40 (48 hr)	"
Loach	10 cm		160 (48 hr)	"
Toad	tadpoles		68 (48 hr)	"
Amer. Crayfish	11 cm		10-40 (72 hr)	"
Water Flea (spp.)	F (adult)		>40 (3 hr)	"

a/ TLm = Median tolerance limit
b/ Soft water, 19.0 ppm hardness
c/ Hard water, 77.1 ppm hardness

In a series of experiments, Rowe et al, (1952) investigated the acute toxicity by oral, dermal, eye contact, and inhalation routes in several laboratory animals. Their findings of acute oral toxicity are summarized in Table 12 and, by the inhalation route, in Table 13. Their conclusions were that EDB caused obvious pain and reversible injury to the rabbit eye and, when confined against the rabbit skin, caused severe burns. Rats and guinea pigs subjected to a single inhalation exposure at concentrations above the 50% mortality level showed CNS depression. Death from respiratory or cardiac failure generally occurred within 24 hours. Death in these same species exposed at concentrations below the 50% mortality level was usually delayed up to 12 days after exposure and was due mostly to pneumonia.

Rabbits, monkeys, rats and guinea pigs, subjected to daily seven-hour exposures, five days a week for approximately six months tolerated 25 ppm without adverse effects. A concentration of 50 ppm was not well tolerated by any of the four species. The most important toxic effects resulting from repeated exposures were irritation of the lungs and injury to the liver and kidneys (Rowe, et al, 1952).

In other studies, Dow scientists demonstrated that potentiation occurs in albino rats after ingestion of mixtures containing EDB, carbon tetrachloride and ethylene dichloride but not after inhalation of these same mixtures. There appears to be a synergistic effect of these mixtures with "pure" EDB being less toxic than all mixtures tested (Adams, et al, 1952; McCollister, et al, 1956; Rowe, et al, 1954).

The NIOSH criteria document (1977) cites an unpublished study by Ter Haar in which ten female and ten male B6C3F1 mice were exposed in inhalation chambers at each of 3 concentrations (3, 15, 75 ppm) of EDB for 6 hrs/d, 5 d/wk for 13 weeks. Ter Haar reported 40% mortality among the male mice at 3 ppm during the 13 weeks and one moribund female in the fifth week at 75 ppm; all other mice survived. Histopathology in respiratory tissues was reported at the 75 ppm level only.

Table 13 - Summary of effects of multiple EDB inhalation exposures in animals (adapted from data of Rowe, et al, 1952).

Species	Sex	Total No. of Animals Used	Conc., No., and Duration of Exposure	Observed Effects
Rats	F	10	100 ppm 7 hr/d x 7 exp. in 9 d	weight loss, increased weight of kidneys, lungs and liver; cloudy swellings of liver and congestion of spleen; lung irritation; blood in stomach; 3/10 deaths
Rats	F M	20 20	50 ppm 7 hr/d x 63 exp. in 91 d	increased weight of kidneys, lungs and liver; decreased weight of testes and spleen
Rats	F	18	50 ppm 7 hr/d x 12 exp. in 16 d	significant increase in liver and kidney weight but no histopathology
Rats	F M	20 20	25 ppm 7 hr/d x 151 exp. in 213 d	12/40 deaths mostly due to pneumonia
Rats	F	23	25 ppm 7 hr/d x 13 exp. in 17 d	no adverse effects reported
Guinea Pigs	F M	8 8	50 ppm 7 hr/d x 57 exp. in 80 d	weight loss; decreased rate of growth; congestion and parenchymatous degeneration of kidneys; fatty degeneration of liver; no effect on testes reported
Guinea Pigs	F	7	50 ppm 7 hr/d x 13 exp. in 17 d	Depressed weight gain; no other adverse effect

Table 13 (Continued) - Summary of effects of multiple EDB inhalation exposures in animals (adapted from data of Rowe, et al, 1952).

Species	Sex	Total Number of Animals Used	Conc. No., and Duration of exposure	Observed Effects
Guinea Pigs	F M	8 8	25 ppm (mg/kg) 7 hr/d x 145 exp. in 205 d	6/16 deaths because of pulmonary infections
Guinea Pigs	F	8	25 ppm 7 hr/d x 13 exp. in 17 d	no adverse effects reported
Rabbits	F	4	100 ppm 7 hr/d x 2-4 exp. in 2-4 days	fatty degeneration of liver, 2 deaths at 2nd day, 1 on 3rd day
Rabbits	F M	3 1	50 ppm 7 hr/d x 59 exp. in 84 d	small increase of liver and kidney weights
Rabbits	F M	1 3	25 ppm 7 hr/d x 152 exp. in 214 d	no adverse effects reported
Monkeys	F M	1 1	50 ppm 7 hr/d x 49 exp. in 70 d	increased weight and slight fatty degeneration of liver
Monkeys	F M	1 1	25 ppm 7 hr/d x 156 exp. in 220 d	no adverse effects reported

Schlinke (1969 and 1970) reported on the effects of oral administration of EDB to sheep, calves and chickens. His data is summarized in Table 14.

Table 14. Oral toxicity of EDB to sheep, calves, and chickens (adapted from Schlinke, 1969 and 1970).

Species (N)	Dosage mg/kg/ b.w.	Observed effects
Sheep (1)	50.0	blood cholinesterase activity (CE) 83% of pretreatment value, died in 3 days.[a/]
" (1)	25.0	no ill effects, CE-81%, 6 hrs.
" (1)	25.0	no effect on CE, died in 2 days.[a/]
" (1)	10.0	no ill effects, CE-69%, 6 hrs.
Calf (1)	50.0	CE - 87%, 48 hrs, died in 3 days.[a/]
" (1)	25.0	no ill effects, CE - 80%, 6 hrs.
" (1)	10.0	no ill effects, no effect on CE.
Chicken (5)	200, 10 days	4 died after 2nd dose, one after 3rd dose, anorexia and depression, excess pericardial fluid and liver congestion.
" (5)	100, 10 days	no ill effects, slightly reduced wt. gain.
" (5)	50 10 days.	no ill effects

a/ animals that died showed signs of "stiffness, prostration and anorexia."

The NIOSH criteria document (1977) cites a number of studies on the acute toxicity of EDB to various animal species. Although the value of these studies is limited due to their generally imprecise design and small numbers of test

organisms, they do show a similar pattern of acute toxic effects in a variety of animal species exposed through several routes. These studies and the tested species and routes of exposure include:

Thomas and Yant (1927) - guinea pigs and rats, single inhalation and dermal exposures;

Lucas (1928) - rabbits, single inhalation exposures;

Kochmann (1928) - rabbits and cats, multiple inhalation exposures;

Glaser and Frisch (1929) - guinea pigs, multiple inhalation exposures;

Kistler and Luckhardt (1929) - dogs, single intravenous, inhalation and oral exposures;

Herzbach (1929) - dogs, single inhalation exposures;

Aman, et al (1946) - guinea pigs and rats, multiple oral (gavage) exposures.

External symptomatology and tissue or organ pathology described in these reports generally is similar to that detailed more completely in the human and animal studies summarized on the preceding pages.

B. Chronic Toxicity Criteria

1. Population Reduction of Nontarget or Endangered Species

The Working Group is not aware of any chronic toxicity data which may suggest that the criteria of 162.11(a)(3)(ii)(C), relative to population reductions in nontarget organisms or endangered species, would be exceeded.

2. Teratogenicity

Under the criteria for other chronic or delayed toxic effects in 162.11(a)(3)(ii)(B), the data presented by Short, et al (1976) suggest

that teratogenic effects may occur in both rats and mice. However the Working Group believes that the findings of this study are not sufficient to support an RPAR on teratogenic effects and that additional information on these effects is needed.

In this study, Short and coworkers exposed pregnant rats and mice to EDB at airborne concentrations of 32 ppm for 23 hr/d from day 6 through 15 of gestation. Two other groups of rats and mice were used; one was the untreated control and the other was a restricted diet group. This dose of EDB appeared to be toxic to both rats and mice as evidenced by decreased food consumption and decreased weight gain. Body weight changes were also seen with the restricted diet group. Indices of fetotoxicity were seen for both rats and mice from EDB exposure, e.g., decreased implants per dam, decreased fetuses per dam, decreased fetal weight. Decreases in some of these same parameters were observed in the restricted diet group.

In the rat, the only teratogenic effect attributable to EDB treatment was wavy ribs. This effect was not seen in the restricted diet or control groups and are seldom observed in rats. Wavy ribs may also be an indication that, if the dose is increased, more teratogenic effects may be seen. There was an increase in fourth ventricle hydrocephaly but the significance was less than 0.10. Incidence of 14th ribs seen in all groups was within normal values for rats.

In mice third ventricle hydrocephaly occurred in both the EDB treated and food-restricted groups. When compared to untreated controls, EDB treated mice had an increase incidence of delayed and incompletely ossified bones. However when the EDB mice and restricted diet mice are compared in this regard, a Fisher's Exact Test shows that these incidences are not statistically different (e.g. worst case $p = 0.164$). Thus, delayed ossification may be due to decreased food intake.

Since only one dose level was used and since this dose caused toxic effects in both pregnant rats and mice, little useful regulatory information can be obtained from this study.

C. Lack of Emergency Treatment Criteria

Available information in the EDB criteria document (NIOSH, 1977) suggest that first aid and remedial procedures are available; therefore the criteria in 162.11(a)(3)(iii) are not met or exceeded.

IV. REQUEST FOR INFORMATION

A. Acute Toxicity Criteria -- Humans

Sufficient data nor information are not available to determine whether this risk criteria is met or exceeded.

B. Other Chronic Effects Criteria

The Agency has determined that a data gap exists and seeks further information on the teratogenic effects of EDB exposure. Teratology studies with at least three dose levels are needed in two species via oral and inhalation routes to properly evaluate EDB's teratogenic potential.

C. Human Exposure Data

The Agency lacks sufficient accurate data on levels of EDB to which humans may be exposed. There is a need for more accurate exposure data from EDB residues in foods and feeds, and for data on acute or chronic inhalation and dermal exposures during soil, commodity, and spot fumigation operations. Such data is needed for the Agency to better assess the risks associated with these potential routes of exposure to EDB.

EDB Part VI Bibliography

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